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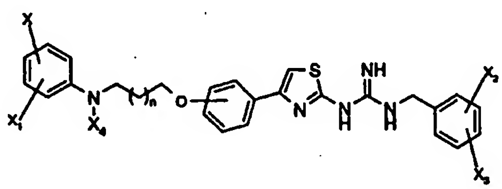

(I)

(57) Abstract

The present invention provides compounds of Formula (I) wherein X, X_1, X_2, and X_3 are independently selected from $-H$, $-C_{1-6}$alkyl, $-C_{1-6}$alkyl substituted by 1–3 fluorines, $-C_{3-7}$cycloalkyl, $-CN$, $-C(O)R_1$, $-C(O)OR_1$, $-C(O)NR_1R_2$, $-C(NR_1)NR_1R_2$, $-C(NCN)NR_1R_2$, $-C(NCN)SR_3$, $-NO_2$, $-NR_1SO_2R_3$, $-NR_1C(O)R_1$, $-NR_1R_2$, $-NR_1(C{=}NR_1)NR_1R_2$, $-NR_1C(O)NR_1R_2$, $-NR_1C(O)R_1$, $-NR_1C(O)OR_3$, $-NR_1C(NCN)SR_3$, $-NR_1C(NCN)NR_1R_2$, $-NR_1C(O)C(O)NR_1R_2$, $-NR_1C(O)C(O)R_2$, $-Cl$, $-Br$, $-I$, $-F$, $-OR_1$, $-O(CH_2)_qOR_3$, $-O(CH_2)_2OH$, $-OC(O)R_1$, $-O(CH_2)_qC(O)NR_1R_2$, $-O(CH_2)_qC(O)R_1$, $-SR_1$, $-SO_2NR_1R_2$ or $-S(O)_mR_3$; m is 0, 1 or 2; q is 1 or 2; n is 0 to 2; R_1 is $-H$, $-C_{1-6}$alkyl, $-CF_3$ or $-CH_2CF_3$; or when R_1 and R_2 are taken together as NR_1R_2, they may together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon and one or more additional heteroatoms selected from O, N, or S; R_2 is H, $-C_{1-6}$alkyl, $-CF_3$ or $-CH_2CF_3$; R_3 is $-C_{1-6}$alkyl, $-CF_3$ or $-CH_2CF_3$; and X_4 is $-H$, $-C_{1-6}$alkyl, $-C_{3-7}$cycloalkyl, $-COAr$, $-COOC_{1-6}$alkyl, or COOAr; which inhibit proteases, including cathepsin K, pharmaceutical compositions of such compounds, and methods for treating diseases of excessive bone loss or cartilage or matrix degradation, including osteoporosis; gingival disease including gingivitis and periodontitis; arthritis, more specifically, osteoarthritis and rheumatoid arthritis; Paget's disease; hypercalcemia of malignancy; and metabolic bone disease therewith.

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PROTEASE INHIBITORS

FIELD OF THE INVENTION

This invention relates in general to thiazoleguanidine protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly compounds which inhibit cysteine proteases, even more particularly compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly compounds which inhibit cysteine proteases of the cathepsin family, most particularly compounds which inhibit cathepsin K. Such compounds are particularly useful for treating diseases in which cysteine proteases are implicated, especially diseases of excessive bone or cartilage loss, e.g., osteoporosis, periodontitis, and arthritis.

BACKGROUND OF THE INVENTION

Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I Collagen represents the major structural protein of bone comprising approximately 90% of the structural protein. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodeling at discrete foci throughout life. These foci, or remodeling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement.

Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. The osteoclasts adhere to the bone surface and form a tight sealing zone, followed by extensive membrane ruffling on their apical (i.e., resorbing) surface. This creates an enclosed extracellular compartment on the bone surface that is acidified by proton pumps in the ruffled membrane, and into which the osteoclast secretes proteolytic enzymes. The low pH of the compartment dissolves hydroxyapatite crystals at the bone surface, while the proteolytic enzymes digest the protein matrix. In this way, a resorption lacuna, or pit, is formed. At the end of this phase of the cycle, osteoblasts lay down a new protein matrix that is subsequently mineralized. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

Several published studies have demonstrated that inhibitors of cysteine proteases are effective at inhibiting osteoclast-mediated bone resorption, and indicate an essential role for a cysteine proteases in bone resorption. For example, Delaisse, *et al.*, *Biochem. J.*, **1980**, *192*, 365, disclose a series of protease inhibitors in a mouse bone organ culture system and suggest that inhibitors of cysteine proteases (e.g., leupeptin, Z-Phe-Ala-CHN_2) prevent bone resorption, while serine protease inhibitors were ineffective. Delaisse, *et al.*, *Biochem. Biophys. Res. Commun.*, **1984**, *125*, 441, disclose that E-64 and leupeptin are also effective at preventing bone resorption *in vivo*, as measured by acute changes in serum calcium in rats on calcium deficient diets. Lerner, *et al.*, *J. Bone Min. Res.*, **1992**, *7*, 433, disclose that cystatin, an endogenous cysteine protease inhibitor, inhibits PTH stimulated bone resorption in mouse calvariae. Other studies, such as by Delaisse, *et al.*, *Bone*, **1987**, *8*, 305, Hill, *et al.*, *J. Cell. Biochem.*, **1994**, *56*, 118, and Everts, *et al.*, *J. Cell. Physiol.*, **1992**, *150*, 221, also report a correlation between inhibition of cysteine protease activity and bone resorption. Tezuka, *et al.*, *J. Biol. Chem.*, **1994**, *269*, 1106, Inaoka, *et al.*, *Biochem. Biophys. Res. Commun.*, **1995**, *206*, 89 and Shi, *et al.*, *FEBS Lett.*, **1995**, *357*, 129 disclose that under normal conditions cathepsin K (which has also been called cathepsin O), a cysteine protease, is abundantly expressed in osteoclasts and may be the major cysteine protease present in these cells.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, selective inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibition of cathepsin K may also be useful for treating diseases of excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix. Thus, selective inhibition of cathepsin K may also be useful for treating certain neoplastic diseases.

Palmer, *et al.*, *J. Med. Chem.*, **1995**, *38*, 3193, disclose certain vinyl sulfones which irreversibly inhibit cysteine proteases, such as the cathepsins B, L, S, O2 and cruzain. Other classes of compounds, such as aldehydes, nitriles, a-ketocarbonyl compounds, halomethyl ketones, diazomethyl ketones, (acyloxy)methyl ketones, ketomethylsulfonium salts and epoxy succinyl compounds have also been reported to inhibit cysteine proteases.

The synthesis of azatides (polyacylhydrazides) as peptide mimetics has recently been disclosed by Han and Janda, *J. Am. Chem. Soc.* **1996**, *118*, 2539.

The synthesis of N-phenyl-N'-(2-phenyloxazol-4-ylcarbonyl)hydrazide, as well as its N-(2,4-dinitrophenyl) derivative, have been described in Afridi, A., et al., *J. Chem. Soc, Perkin Trans. I*, **1976**, *3*, 315-20. Benko, A.,et al., *Justus Liebigs Ann. Chem.*, **1968**, *717*, 148-53 describes the preparation of N-(4-ethoxycarbonylthiazol-2-yl)-N'-[2-(4-pyridinyl)thiazol-4-ylcarbonyl]hydrazide.

Thus, a structurally diverse variety of cysteine protease inhibitors have been identified. However, these known inhibitors are not considered suitable for use as therapeutic agents in animals, especially humans, because they suffer from various shortcomings. These shortcomings include lack of selectivity, cytotoxicity, poor solubility, and overly rapid plasma clearance. A need therefore exists for methods of treating diseases caused by pathological levels of proteases, especially cysteine proteases, including cathepsins, especially cathepsin K, and for novel inhibitor compounds useful in such methods.

We have now discovered a novel class of thiazoleguanidine compounds which are protease inhibitors, most particularly of cathepsin K.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

SUMMARY OF THE INVENTION

An object of the present invention is to provide thiazoleguanidine protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly such compounds which inhibit cysteine proteases, even more particularly such compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly such compounds which inhibit cysteine proteases of the cathepsin family, most particularly such compounds which inhibit cathepsin K, and which are useful for treating diseases which may be therapeutically modified by altering the activity of such proteases.

Accordingly, in the first aspect, this invention provides a compound according to Formula I.

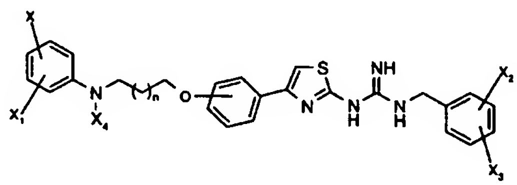
In another aspect, this invention provides a pharmaceutical composition comprising a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient.

In still another aspect, this invention provides methods of treating diseases in which the disease pathology may be therapeutically modified by inhibiting proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, most particularly cathepsin K.

In a particular aspect, the compounds of this invention are especially useful for treating diseases characterized by bone loss, such as osteoporosis and gingival diseases, such as gingivitis and periodontitis, or by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of Formula I:



(I)

wherein:

X, X_1, X_2, and X_3 are independently selected from -H, -C_{1-6}alkyl, -C_{1-6}alkyl substituted by 1-3 fluorines, -C_{3-7}cycloalkyl, -CN, -C(O)R_1, -C(O)OR_1, -C(O)NR_1R_2, -C(NR_1)NR_1R_2, -C(NCN)NR_1R_2, -C(NCN)SR_3, -NO_2, -NR_1SO_2R_3, -NR_1C(O)R_1, -NR_1R_2, -NR_1(C=NR_1)NR_1R_2, -NR_1C(O)NR_1R_2, -NR_1C(O)R_1, -NR_1C(O)OR_3, -NR_1C(NCN)SR_3, -NR_1C(NCN)NR_1R_2, -NR_1C(O)C(O)NR_1R_2, -NR_1C(O)C(O)R_2, -Cl, -Br, -I, -F, -OR_1, -O$(CH_2)_q$OR_3, -O$(CH_2)_2$OH, -OC(O)R_1, -O$(CH_2)_q$C(O)NR_1R_2, -O$(CH_2)_q$C(O)R_1, -SR_1, -SO_2NR_1R_2 or -S$(O)_m R_3$;

m is 0, 1 or 2;

q is 1 or 2;

n is 0 to 2;

R_1 is -H, -C_{1-6}alkyl, -CF_3 or -CH_2CF_3; or when R_1 and R_2 are taken together as NR_1R_2, they may together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon and one or more additional heteroatoms selected from O, N, or S;

R_2 is H, -C_{1-6}alkyl, -CF_3 or -CH_2CF_3;

R_3 is -C_{1-6}alkyl, -CF_3 or -CH_2CF_3; and

X_4 is -H, -C_{1-6}alkyl , -C_{3-7}cycloalkyl, -COAr, -COOC_{1-6}alkyl, or COOAr.

Preferred embodiments of the present invention include compounds of Formula I wherein:

X, X_1, X_2,and X_3 are independently H or halogen;

X_4 is CH_3 or Cbz; and

n=1 or 2.

Yet more preferred embodiments of the present invention include compounds of Formula I wherein:

X, X_1, X_2,and X_3 are independently H or Cl;

X_4 is -CH_3; and

n=1 or 2.

Still more preferred embodiments of the present invention include compounds of Formula I wherein:

X and X_1 are Cl;

X_2,and X_3 are H;

X_4 is CH_3; and

n=1.

The following compounds are particularly preferred embodiments of the present invention:

N-Benzyl-N'-{4-{3-[4-(N-methyl-N-phenyl)aminobutoxy]phenyl}thiazol-2-yl}guanidine;

N-Benzyl-N'-{4-{3-[4-(N-(3,4-dichlorophenyl-N-methyl)aminopropoxy]phenyl}thiazol-2-yl}guanidine;

N-Benzyl-N'-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine;

N-Benzyl-N'-{4-[3-(4-N-piperazinobutoxy)phenyl]thiazol-2-yl}guanidine;

N-Benzyl-N'-{4-{4-[3-(N-(3,4-dichlorophenyl)-N-methyl)aminopropoxy]phenyl}thiazol-2-yl}urea; and

N-Benzyl-N'-{4-{4-[3-[N-carbobenzyloxy-N-(3,4-dichlorophenyl)]aminopropoxy]phenyl}thiazol-2-yl}guanidine

Definitions

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds which release the active parent drug according to Formula I *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984). The term "amino acid" as used herein refers to the D- or L- isomers of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

"C_{1-6}alkyl" as applied herein is meant to include substituted and unsubstituted methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl, pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. Any C_{1-6}alkyl group may be

optionally substituted independently by one or two halogens, SR', OR', $N(R')_2$, $C(O)N(R')_2$, carbamyl or C_{1-4}alkyl, where R' is C_{1-6}alkyl. C_0alkyl means that no alkyl group is present in the moiety. Thus, Ar-C_0alkyl is equivalent to Ar.

"C_{3-7}cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane, cyclohexane, and cycloheptane. When substituted, substituents are defined as for "C_{1-6}alkyl", above.

"Halogen" means F, Cl, Br, and I.

"Ar" or "aryl" means phenyl or naphthyl, optionally independently substituted by one or more of Ph-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, Ph-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, $(CH_2)_{1-6}NR_4R_5$, $O(CH_2)_{1-6}NR_4R_5$, CO_2R', or halogen. R_4 and R_5 are independently H, C_{1-6}alkyl, C_{2-6}alkenyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl. Two C_{1-6}alkyl groups may be combined to form a 5-7 membered ring, saturated or unsaturated, fused onto the Ar ring. Ph may be optionally substituted with one or more of C_{1-6}alkyl, C_{1-6}alkoxy, OH, $(CH_2)_{1-6}N\ R_4R_5$, $O(CH_2)_{1-6}N\ R_4R_5$, CO_2R', or halogen.

As used herein "Het" or "heterocyclic", and "when R_1 and R_2 are taken together as NR_1R_2, they may together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon and one or more additional heteroatoms selected from O, N, or S", represent a stable 5- to 7-membered heterocyclic ring, which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure, and may optionally be substituted with one or two moieties selected from the group consisting of Ph-C_{0-6}alkyl, Het-C_{0-6} alkyl, C_{1-6}alkyl, C_{1-6}alkoxy, Ph-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, $(CH_2)_{1-6}NR_4R_5$, $O(CH_2)_{1-6}NR_4R_5$, CO_2R'. Two C_{1-6}alkyl groups may be combined to form a 5-7 membered ring, saturated or unsaturated, fused onto the Het ring. Ph may be optionally substituted with one or more of C_{1-6}alkyl, C_{1-6}alkoxy, OH, $(CH_2)_{1-6}NR_4R_5$, $O(CH_2)_{1-6}NR_4R_5$, CO_2R', or halogen. Examples of such heterocycles include the piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl,

benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl rings.

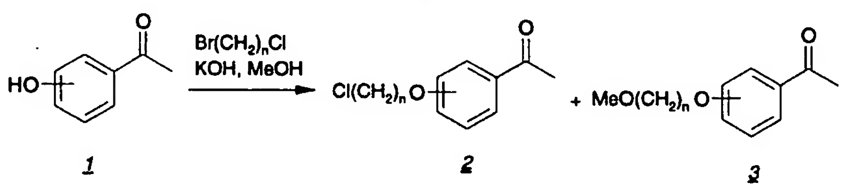
Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical.

Certain reagents are abbreviated herein. DMAP refers to dimethylaminopyridine, DMF refers to dimethyl formamide, TFA refers to trifluoroacetic acid, and THF refers to tetrahydrofuran.

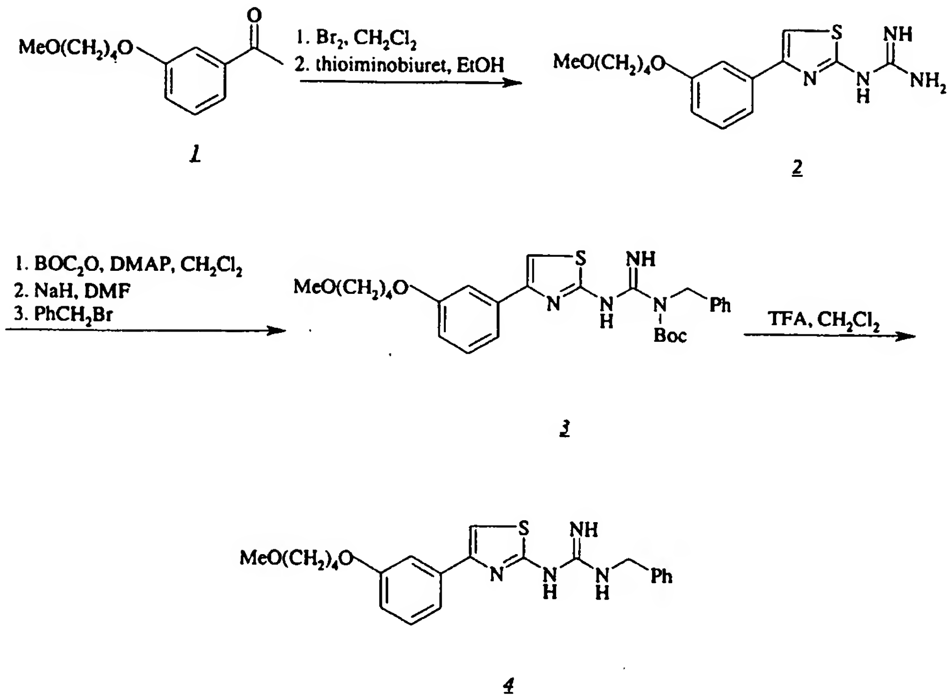
Methods of Preparation

Hydroxyacetophenones 1-Scheme 1 may be alkylated by treatment with an a,w-dihaloalkane, such as 1-bromo-3-chloropropane and a suitable base, such as potassium hydroxide, in an appropriate solvent, such as refluxing methanol. When methanol is the chosen solvent, a small amount of methoxyalkoxy-acetophenone 2-Scheme 1 may also be isolated as a by-product.

Scheme 1

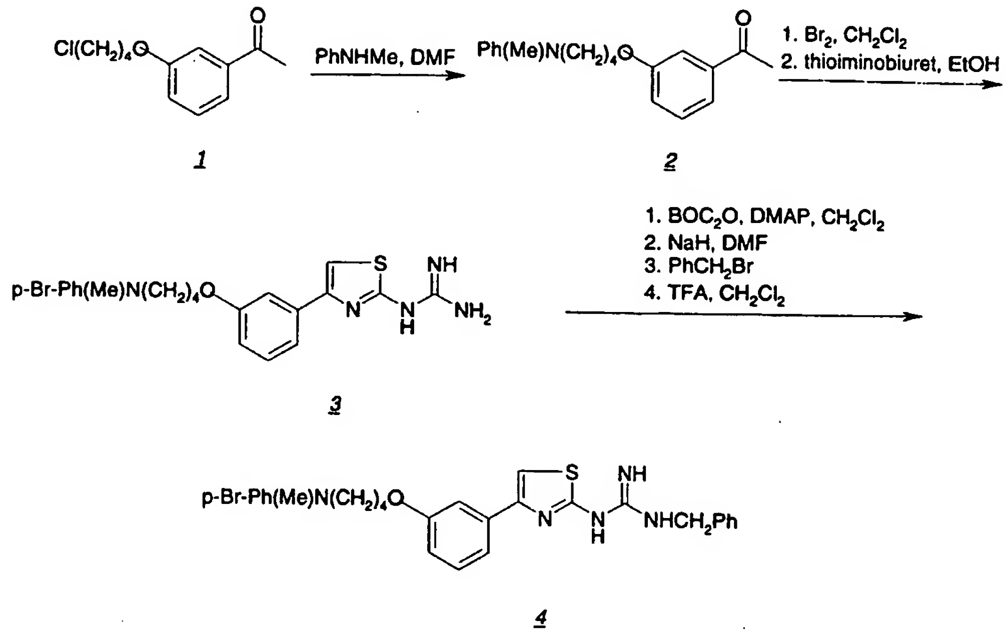


Scheme 2



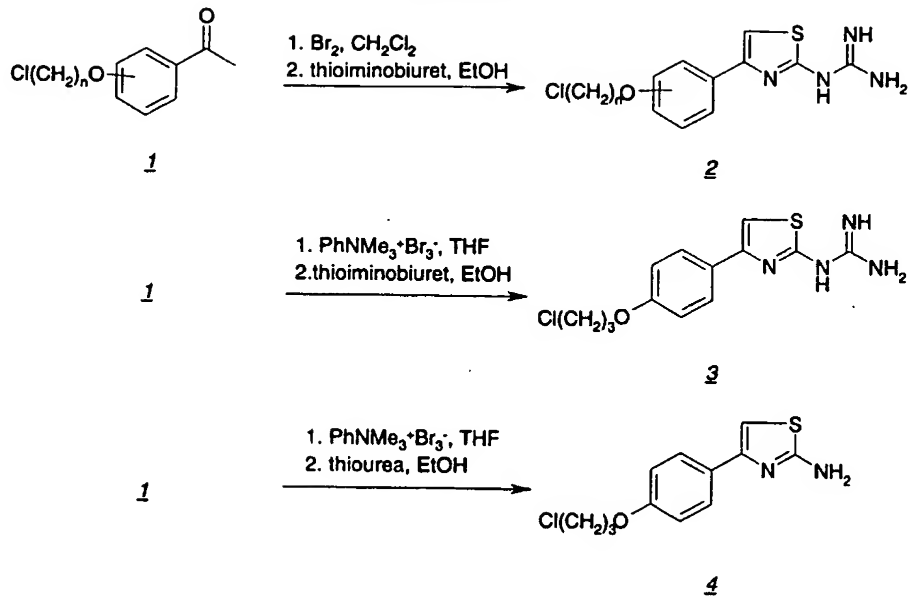
3-(4-Methoxybutoxy)acetophenone 1-Scheme 2 may be transformed to the thiazoleguanidine 2-Scheme 2 by treatment first with an appropriate brominating agent, such as bromine, in a halogenated solvent, such as dichloromethane, followed by reaction with 2-imino-4-thiobiuret in a refluxing alcoholic solvent, such as ethanol. The guanidine group is activated towards alkylation by preparing a suitable derivative, for example the *t*-butoxycarbonylguanidine, which can be formed by treating the compound 2-Scheme 2 with the appropriate carbamylating reagent, such as di-*t*-butyldicarbonate, under appropriate conditions, such as dichloromethane solvent with dimethylaminopyridine coreagent. Alkylation of the activated guanidine can then proceed by deprotonation with a suitable base, especially sodium hydride, in a suitable solvent, such as dimethylformamide, followed by addition of the desired alkylating agent, in this example, benzyl bromide, provides compound 3-Scheme-2. Deprotection of the guanidine, with, for example, trifluoroacetic acid in dichloromethane, provides the final product 4-Scheme 2.

Scheme 3



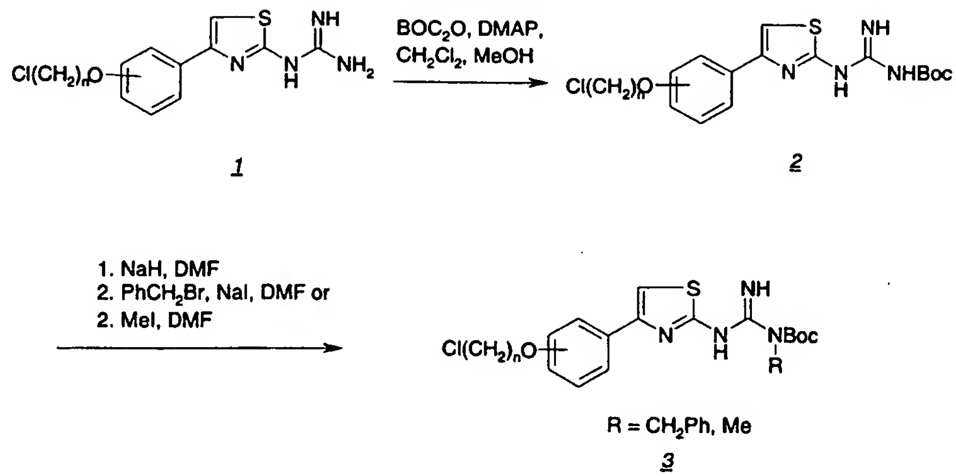
Alternatively, 3-(4-chlorobutoxy)acetophenone 1-Scheme 3 may be used to alkylate an aniline, in this example N-methylaniline, in a suitable solvent, such as dimethylformamide or nitromethane at high heat. The resulting acetophenone 2-Scheme 3 may be transformed to the thiazoleguanidine 3-Scheme 3 by treatment first with an appropriate brominating agent, such as bromine in a halogenated solvent, such as dichloromethane, followed by reaction with 2-imino-4-thiobiuret in a refluxing alcoholic solvent, such as ethanol. The bromination conditions lead to *para*-bromination of the aniline ring as well as formation of the α-bromoketone intermediate. The guanidine group is then activated towards alkylation by forming a suitable derivative, for example the *t*-butoxycarbonylguanidine, which can be formed by treating the compound 3-Scheme 3 with the appropriate carbamylating reagent, such as di-*t*-butyldicarbonate, under appropriate conditions, such as dichloromethane solvent with dimethylaminopyridine coreagent. Alkylation of the activated guanidine can then proceed by deprotonation with a suitable base, especially sodium hydride in a suitable solvent, such as dimethylformamide, followed by addition of the desired alkylating agent, in this example, benzyl bromide. Deprotection of the guanidine, with, for example, trifluoroacetic acid in dichloromethane, provides the final product 4-Scheme 3.

Scheme 4



Various reaction conditions have been found to be effective in thiazole formation. For example, as described above, treatment of chloroalkoxy-acetophenone 1-Scheme 4 with bromine in an appropriate halogenated solvent, such as dichloromethane, followed by treatment with 2-imino-4-thiobiuret in a refluxing alcoholic solvent, such as ethanol, provides the 4-(chloroalkoxyphenyl)-2-guanidylthiazoles 2-Scheme 4. Using the same reaction conditions, except changing the bromination conditions by using a different brominating reagent, such as phenyltrimethylammonium tribromide, in a suitable solvent, such as tetrahydrofuran, provides 4-[4-(3-chloropropoxy)phenyl]-2-guanidylthiazole 3-Scheme 4. Using the same reaction conditions, except substituting thiourea for 2-imino-4-thiobiuret, allows preparation of aminothiazoles, for example 2-amino-4-[4-(3-chloropropoxy)phenyl]thiazole 4-Scheme 4.

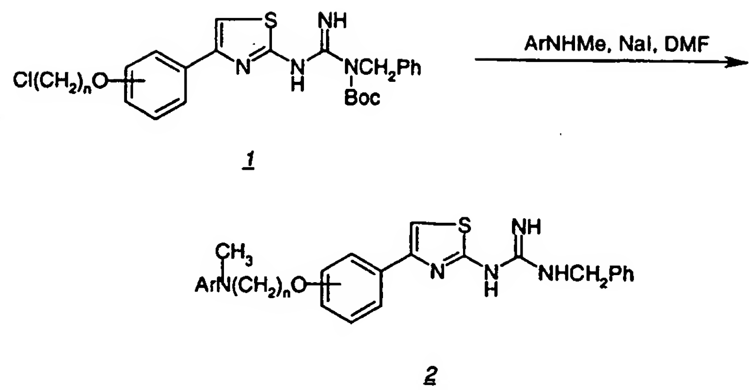
Scheme 5



The monosubstituted guanidine 1-Scheme 5 is activated towards alkylation by formation of a suitable derivative, such as a carbamate, especially the *t*-butyoxycarbonylguanidine 2-Scheme 5, which is formed by reaction with a suitable carbamylating reagent , such as di-*t*-butyldicarbonate, under appropriate reaction conditions, such as using dimethylaminopyridine as a coreagent and dichloromethane-methanol as the solvent. The *t*-butoxycarbonylguanidine 2-Scheme 5 may be deprotonated with a suitable base, such as sodium hydride, in an appropriate solvent, such as dimethylformamide, followed by treatment with an alkylating reagent, for example with methyl iodide or with benzyl bromide and added sodium iodide, to provide the desired *t*-butoxycarbonyl-protected disubstituted guanidine 3-Scheme 5.

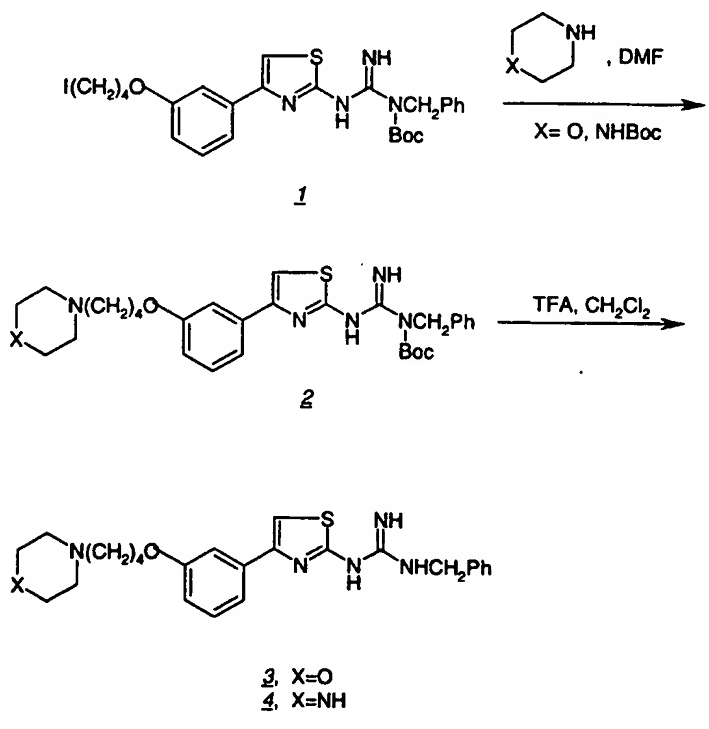
The chloroalkoxyaromatic 1-Scheme 6 may be used to alkylate an aniline, for example N-methylaniline in a suitable solvent, especially dimethylformamide, acetonitrile or nitromethane, at high heat, with or without the addition of sodium iodide. These reaction conditions also cause the removal of the *t*-butoxycarbonyl group to provide the final products 2-Scheme 6. Alternatively, one of many

Scheme 6



halogen exchange reactions, such treatment with sodium iodide in refluxing acetone, may precede the anilination reaction.

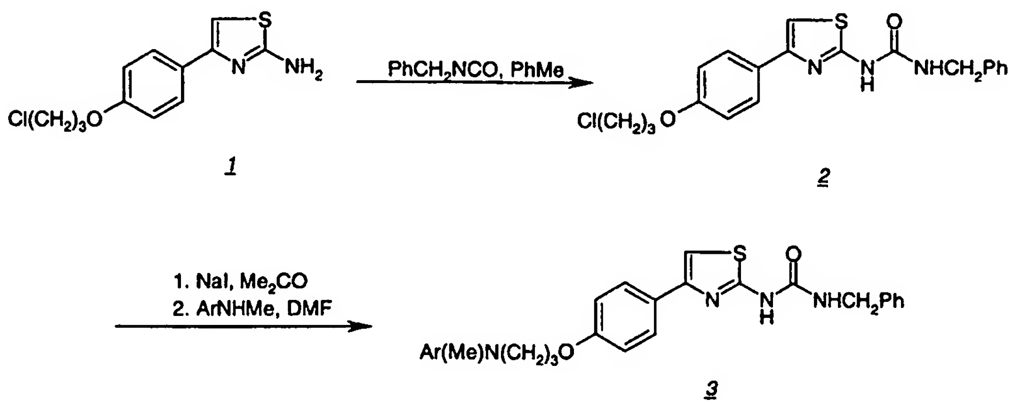
Scheme 7



The iodobutoxyaromatic 1-Scheme 7 may be reacted with a secondary amine, in these examples with morpholine or N-*t*-butoxycarbonylpiperazine, in a suitable solvent,

such as dimethylformamide at high heat to provide the aminated compounds 2-Scheme 7. Deprotection of the *t*-butoxycarbonyl group(s) under suitable conditions, especially trifluoroacetic acid in dichloromethane, provides the final compounds 3-Scheme 7 and 4-Scheme 7.

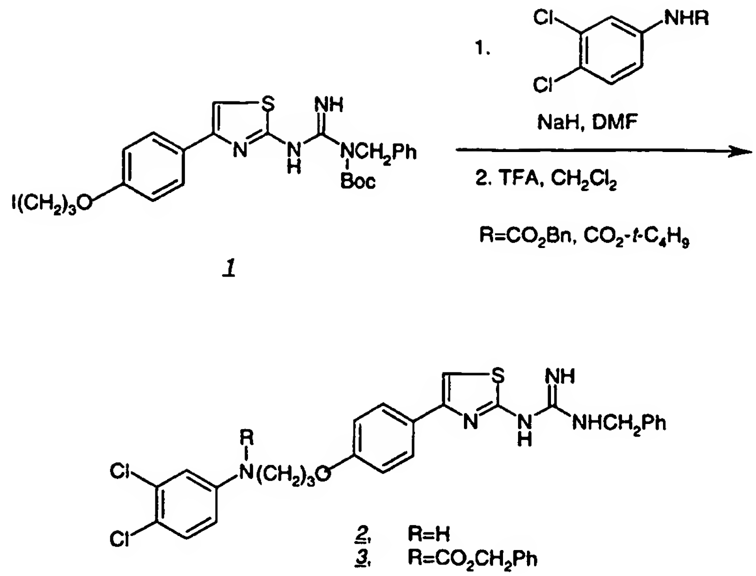
Scheme 8



Aminothiazole 1-Scheme 8 may be treated with an isocyanate, such as benzyl isocyanate in an appropriate solvent, such as refluxing toluene, to provide the substituted thiazole urea 2-Scheme 8. Halogen exchange under suitable reaction conditions, especially treatment with sodium iodide in refluxing acetone, followed by reaction with an N-methylaniline in an appropriate solvent, such as dimethylformamide or nitromethane, at high heat, provides the desired compound 3-Scheme 8.

The iodopropoxyaromatic 1-Scheme 9 may be treated with the anion of a carbamate, especially the benzyl or *t*-butyl carbamates, of 3,4-dichloroaniline to prepare the anilinated intermediate. The anion may be formed by treatment of the protected aniline with a suitable base, for example a butyllithium or a metal hydride, especially sodium hydride, in a suitable solvent, such as tetrahydrofuran or dimethyformamide, especially dimethylformamide. Removal of the *t*-butoxycarbonyl group(s) may be achieved by treatment of the intermediate with suitable reagents, such as trifluoroacetic acid in the appropriate solvent, such as dichloromethane to provide the disubstituted aniline 2-Scheme 9 and the benzylcarbamate substituted analog 3-Scheme 9.

Scheme 9



The starting materials used herein are commercially available amino acids or are prepared by routine methods well known to those of ordinary skill in the art and can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

Coupling methods to form amide bonds herein are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984; E. Gross and J. Meienhofer, THE PEPTIDES, Vol. 1, 1-284 (1979); and J.M. Stewart and J.D. Young, SOLID PHASE PEPTIDE SYNTHESIS, 2d Ed., Pierce Chemical Co., Rockford, Ill., 1984. are generally illustrative of the technique and are incorporated herein by reference.

Synthetic methods to prepare the compounds of this invention frequently employ protective groups to mask a reactive functionality or minimize unwanted side reactions. Such protective groups are described generally in Green, T.W, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York (1981). The term "amino protecting groups" generally refers to the Boc, acetyl, benzoyl, Fmoc and Cbz groups and derivatives thereof as known to the art. Methods for protection and deprotection, and replacement of an amino protecting group with another moiety are well known.

Acid addition salts of the compounds of Formula I are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as

hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+, Na^+, K^+, Ca^{++}, Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts. Halides, sulfate, phosphate, alkanoates (such as acetate and trifluoroacetate), benzoates, and sulfonates (such as mesylate) are examples of anions present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a compound according to Formula I and a pharmaceutically acceptable carrier, diluent or excipient. Accordingly, the compounds of Formula I may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of Formula I prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and

compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

Utility of the Present Invention

The thiazoleguanidines of this invention are uncompetitive inhibitors that are comparatively poor inhibitors at low substrate concentrations. More specifically, we have discovered that these compounds display a dual mode of inhibition:

1) Induced substrate inhibition in the presence of substrate (that is, the protein which the enzyme degrades or otherwise operates on) wherein at higher K_m levels of substrate, the present compounds induce the substrate to become an inhibitor of the enzyme. Thus, the present thiazoleguanidines appear to bind exclusively to an enzyme form that has already bound substrate; and 2) Double inhibition studies with the present thiazoleguanidines and exemplary protease inhibitors that are active-site directed, mechanism-based inhibitors (most particularly of cathepsin K, as disclosed in International Publication No. WO 97/16433, having an International Publication Date of May 9, 1997) show that the present compounds and the mechanism-based inhibitors can both bind at the same time and enhance each other's binding.

The compounds of Formula I are useful as protease inhibitors. The compounds of Formula I are particularly useful as inhibitors of cysteine and serine proteases, more particularly as inhibitors of cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly as inhibitors of cysteine proteases of the cathepsin family, most particularly as inhibitors of cathepsin K. The present invention also provides useful compositions and formulations of said compounds, including pharmaceutical compositions and formulations of said compounds.

The present compounds are useful for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy; and especially diseases in

which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease; hypercalcemia of malignancy, and metabolic bone disease.

Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix, and certain tumors and metastatic neoplasias may be effectively treated with the compounds of this invention.

The present invention also provides methods of treatment of diseases caused by pathological levels of proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family. These methods comprise administering to an animal, particularly a mammal, most particularly a human, in need thereof an effective amount of a compound or combination of compounds of the present invention, optionally together with an effective amount of an active-site directed, mechanism-based inhibito, the enzyme inhibition properties of which are capable of being augmented by the presence of the inventive compounds. Exemplary such inhibitors are disclosed in International Publication No. WO 97/16433, having an International Publication Date of May 9, 1997. The present invention especially provides methods of treatment of diseases caused by pathological levels of cathepsin K, which methods comprise administering to an animal, particularly a mammal, most particularly a human, in need thereof an effective amount of a compound or combination of compounds of the present invention, optionally together with an effective amount of an active-site directed, mechanism-based inhibitor (for instance, as disclosed in International Publication No. WO 97/16433, having an International Publication Date of May 9, 1997), the enzyme inhibition properties of which are capable of being augmented by the presence of the inventive compounds. The skilled artisan will understand that by the term "effective amount" is meant that amount of a compound or combination of compounds of the present invention sufficient to ameliorate or cure the clinically undesirable manifestations of disease (e.g. brittle and weakened bone in osteoporosis) caused by said pathological levels of target enzyme, e.g., cathepsin K, by inhibition of the target enzyme. The present invention particularly provides methods for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis,

metachromatic leukodystrophy, muscular dystrophy, amytrophy, and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease.

This invention further provides a method for treating osteoporosis or inhibiting bone loss which comprises internal administration to an animal, particularly a mammal, most particularly a human in need thereof an effective amount of a compound or combination of compounds of Formula I, optionally together with an effective amount of an inhibitor of cathepsin K capable of being augmented by the presence of the inventive co-inhibitors (for instance, as disclosed in International Publication No. WO 97/16433, having an International Publication Date of May 9, 1997), optionally in combination with other inhibitors of bone resorption, such as bisphosphonates (i.e., allendronate), hormone replacement therapy, anti-estrogens, or calcitonin. In addition, treatment with a compound of this invention, optionally together with an effective amount of an inhibitor of cathepsin K capable of being augmented by the presence of the inventive compounds(for instance, as disclosed in International Publication No. WO 97/16433, having an International Publication Date of May 9, 1997), and an anabolic agent, such as bone morphogenic protein, iproflavone, may be used to prevent bone loss or to increase bone mass.

For acute therapy, parenteral administration of a compound of Formula I, optionally simultaneously or sequentially with an effective amount of a protease inhibitor capable of being augmented by the presence of the inventive compounds (for instance, as disclosed in International Publication No. WO 97/16433, having an International Publication Date of May 9, 1997) is preferred. An intravenous infusion of the inventive compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit cathepsin K. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise amount of an inventive compound which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary

skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of this invention may also be administered orally to the patient, optionally simultaneously or sequentially with an effective amount of a protease inhibitor capable of being augmented by the presence of the inventive compounds (for instance, as disclosed in International Publication No. WO 97/16433, having an International Publication Date of May 9, 1997), in a manner such that the concentration of drug is sufficient to inhibit bone resorption or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

Biological Assays

The compounds of the present invention may be tested in one of several biological assays to determine the concentration of compound which is required to provide a given pharmacological effect.

Determination of cathepsin K proteolytic catalytic activity

All assays for cathepsin K were carried out with human recombinant enzyme. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically Cbz-Phe-Arg-AMC, and were determined in 100 mM Na acetate at pH 5.5 containing 20 mM cysteine and 5 mM EDTA. Stock substrate solutions were prepared at concentrations of 10 or 20 mM in DMSO with 20 uM final substrate concentration in the assays. All assays contained 10% DMSO. Independent experiments found that this level of DMSO had no effect on enzyme activity or kinetic constants. All assays were conducted at ambient temperature. Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored with a Perceptive Biosystems Cytofluor II fluorescent plate reader. Product progress curves were generated over 20 to 30 minutes following formation of AMC product.

Inhibition studies

Potential inhibitors were evaluated using the progress curve method. Assays were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were calculated according to equation 1 (Brandt *et al.*, *Biochemitsry,* **1989**, *28*, 140):

$$v = V_m A / [K_a(1 + I/K_{i,\ app}) + A] \qquad (1)$$

where v is the velocity of the reaction with maximal velocity V_m , A is the concentration of substrate with Michaelis constant of K_a, and I is the concentration of inhibitor.

For those compounds whose progress curves showed downward curvature characteristic of time-dependent inhibition, the data from individual sets was analyzed to give k_{obs} according to equation 2:

$$[\mathrm{AMC}] = v_{ss}\, t + (v_0 - v_{ss})\, [1 - exp\,(-k_{obs}t)] / k_{obs} \qquad (2)$$

where [AMC] is the concentration of product formed over time t, v_0 is the initial reaction velocity and v_{ss} is the final steady state rate. Values for k_{obs} were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant (k_{obs} / inhibitor concentration or k_{obs} / [I]) describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **1988**, *61*, 201).

Human Osteoclast Resorption Assay

Aliquots of osteoclastoma-derived cell suspensions were removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000 rpm, 5 min at 4°C). The medium was aspirated and replaced with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium, and incubated for 30 min on ice The cell suspension was mixed frequently.

The cells were washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5 min at 4°C) and then transferred to a sterile 15 mL centrifuge tube. The number of mononuclear cells were enumerated in an improved Neubauer counting chamber.

Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, were removed from their stock bottle and placed into 5 mL of fresh medium (this washes away the toxic azide preservative). The medium was removed by immobilizing the beads on a magnet and is replaced with fresh medium.

The beads were mixed with the cells and the suspension was incubated for 30 min on ice. The suspension was mixed frequently. The bead-coated cells were immobilized on a magnet and the remaining cells (osteoclast-rich fraction) were decanted into a sterile 50 mL centrifuge tube. Fresh medium was added to the bead-coated cells to dislodge any trapped osteoclasts. This wash process was repeated x10. The bead-coated cells were discarded.

The osteoclasts were enumerated in a counting chamber, using a large-bore disposable plastic pasteur pipette to charge the chamber with the sample. The cells were pelleted by centrifugation and the density of osteoclasts adjusted to 1.5×10^4/mL in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate. 3 mL aliquots of the cell suspension (per treatment) were decanted into 15 mL centrifuge tubes. These cells were pelleted by centrifugation. To each tube 3 mL of the appropriate treatment was added (diluted to 50 uM in the EMEM medium). Also included were appropriate vehicle controls, a positive control (87MEM1 diluted to 100 ug/mL) and an isotype control (IgG2a diluted to 100 ug/mL). The tubes were incubate at 37°C for 30 min.

0.5 mL aliquots of the cells were seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 h. Each treatment was screened in quadruplicate. The slices were washed in six changes of warm PBS (10 mL / well in a 6-well plate) and then placed into fresh treatment or control and incubated at 37°C for 48 h. The slices were then washed in phosphate buffered saline and fixed in 2% glutaraldehyde (in 0.2M sodium

cacodylate) for 5 min., following which they were washed in water and incubated in buffer for 5 min at 37°C. The slices were then washed in cold water and incubated in cold acetate buffer / fast red garnet for 5 min at 4°C. Excess buffer was aspirated, and the slices were air dried following a wash in water.

The TRAP positive osteoclasts were enumerated by bright-field microscopy and were then removed from the surface of the dentine by sonication. Pit volumes were determined using the Nikon/Lasertec ILM21W confocal microscope.

General

Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (d) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

Where indicated, certain of the materials were purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, Chemical Dynamics Corp., South Plainfield, New Jersey, and Advanced Chemtech, Louisville, Kentucky.

Examples

In the following synthetic examples, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

Example 1

N-Benzyl-N'-{4-{3-[4-(N-methyl-N-phenyl)aminobutoxy]phenyl}thiazol-2-yl}guanidine.

1a. 3-(4-Chlorobutoxy)acetophenone

A solution of 3-hydroxyacetophenone (5.07 g, 37 mmol) and 1-bromo-4-chlorobutane (12.0 mL, 104 mmol) in methanol (25 mL) at room temperature was treated portionwise with potassium hydroxide (6.3 g, 112 mmol). The thick white suspension was stirred at reflux for 24 h and was cooled. The reaction mixture was filtered through Celite, washing well with ether, and the filtrate was evaporated. The residue was dissolved in ether, was washed twice with water and once with brine, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 1:9 ethyl acetate:hexanes, provided 3-(4-chlorobutoxy)acetophenone (7.29 g, 87%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.54 (d, J=7.8 Hz, 1H), 7.47 (t, J=2.0 Hz, 1H), 7.37 (t, J=7.9 Hz, 1H), 7.10 (dd, J=2.3, 7.8 Hz, 1H), 4.05 (t, J=5.6 Hz, 2H), 3.63 (t, J=6.1 Hz, 2H), 2.60 (s, 3H), 1.99 (m, 4H) ppm.

Also isolated as a byproduct was 3-(4-methoxybutoxy)acetophenone (0.60 g, 8%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.52 (dd, J=0.9, 6.8 Hz, 1H) 7.47 (t, J=2.0 Hz, 1H), 7.36 (t, J=7.9 Hz, 1H), 7.10 (dd, J=2.2, 7.9 Hz), 4.04 (t, J=6.3 Hz, 2H), 3.45 (t, J=6.4 Hz, 2H), 3.35 (s, 3H), 2.59 (s, 3H), 1.88 (m, 4H) ppm.

1b. N-{4-[3-(4-Chlorobutoxy)phenyl]thiazol-2-yl}guanidine

A solution of 3-(4-chlorobutoxy)acetophenone (1.0 g, 4.41 mmol) in dichloromethane (15 mL) at room temperature was treated dropwise over 5 min with a solution of bromine (0.225 mL, 4.41 mmol) in dichloromethane (5 mL), was stirred for 15 min, and was evaporated. The residue was dissolved in absolute ethanol (25 mL), was treated with iminothiobiuret (0.52 g, 4.41 mmol), was refluxed for 24 h, was cooled and was evaporated. Purification by flash chromatography, eluting with 5:95 methanol:dichloromethane, provided N-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine (1.15 g, 80%) as a tan solid, m.p.126-129°C.

1c. N-*t*-Butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine

A mixture of N-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine (1.15 g, 4.47 mmol), di-*t*-butyldicarbonate (1.68 g, 9.84 mmol) and several crystals of 4-(N,N-dimethylamino)pyridine in dichloromethane (20 mL) was stirred at room temperature under argon for 3 d. The reaction was evaporated and was purified by flash chromatography, eluting with 15:85 ethyl acetate:hexanes, to obtain N-*t*-butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine (0.85 g, 45%) as a white foam, m.p. 53-56°C.

1d. N-Benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine

A mixture of N-*t*-butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine (0.45 g, 1.05 mmol) and 60% sodium hydride/mineral oil suspension (0.046 g, 1.16 mmol) in dimethylformamide (5 mL) was stirred at room temperature under argon for 0.5 h, then was treated with benzyl bromide (0.14 mL, 1.16 mmol) and sodium iodide (0.015 g, 10 %) and was stirred for 24 h. The reaction was diluted with water and was extracted twice with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 1:9 ethyl acetate:hexanes, provided N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine (0.24 g, 43%) as a white wax, m.p. 71-73°C.

1e. N-Benzyl-N'-{4-{3-[4-(N-methyl-N-phenyl)aminobutoxy]phenyl}thiazol-2-yl}guanidine

A solution of N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine (0.18 g, 0.35 mmol), N-methylaniline (0.075 mL, 0.70 mmol) and sodium iodide (0.05 g, 0.35 mmol) in dimethylformamide was stirred at 130-135°C for 4 d and was cooled. The reaction was diluted with water and was extracted twice with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate), and was evaporated. Purification by flash chromatography, eluting with 35:65 ethyl acetate:hexanes, provided the title compound (0.060 g, 36%) as a pale amber glass, m.p. 41-43°C.
Analysis calc. for $C_{28}H_{31}N_5OS \cdot 0.3\ H_2O$: C 68.49, H 6.49, N 14.26: found: C 68.44, H 6.33, N 13.95.

Proceeding in the same manner as in Example 1, but substituting the appropriate intermediates for those described above, the following compounds were made as set forth in Examples 2-7 below:

Example 2

N-Methyl-N'-{4-{3-[4-(N-methyl-N-phenyl)aminobutoxy]phenyl}thiazol-2-yl}guanidine

Analysis calc. for $C_{22}H_{27}N_5OS$: C 64.52, H 6.65, N 17.10: found: C 64.44, H 6.59, N 16.69, m.p. 44-48°C.

Example 3

N-Benzyl-N'-{4-{3-[4-(N-(3,4-dichlorophenyl)-N-methyl)aminobutoxy]phenyl}thiazol-2-yl}guanidine

Analysis calc. for $C_{28}H_{29}Cl_2N_5OS$: C 60.65, H 5.27, N 12.63: found: C 60.78, H 5.45, N 12.32., , m.p.43-47°C.

Example 4

N-(3,4-Dichlorobenzyl)-N'-{4-{3-[4-(N-(3,4-dichlorophenyl)-N-methyl)aminobutoxy]phenyl}thiazol-2-yl}guanidine

Mass Spec.(ES+): M+H (621.9, 624.2, 624.3, 626.2), m.p. 41-49°C.

Example 5

N-Benzyl-N'-{4-{3-[3-(N-(3,4-dichlorophenyl)-N-methyl)aminopropoxy]phenyl}thiazol-2-yl}guanidine

Mass Spec (ES+): M+H (540.2, 542.1), m.p. 56-60°C.

Example 6

N-Benzyl-N'-{4-{4-[3-(N-(3,4-dichlorophenyl)-N-methyl)aminopropoxy]phenyl}thiazol-2-yl}guanidine

Mass Spec. (ES+): M+H (540.2, 542.2), ^{1}H-NMR ($CDCl_3$, 400 MHz) : δ 7.56 (br, 2H), 7.41 (m, 6H), 7.19 (d, J=9.1 Hz, 1H), 6.85 (d, J=9.0Hz, 2H), 6.76 (d, J=2.7 Hz, 1H), 6.74 (s, 1H), 6.53 (dd, J=2.8, 9.1 Hz, 1H), 4.52 (s, 2H), 3.99 (t, J=5.7 Hz, 2H), 3.53 (t, J=6.8 Hz, 2H), 2.92 (s, 3H), 2.04 (t, J=6.4 Hz, 2H) ppm.

Example 7

N-Benzyl-N'-{4-{4-[3-(N-methyl-N-phenyl)aminopropoxy]phenyl}thiazol-2-yl}guanidine

Analysis calc. for $C_{27}H_{29}N_5OS \cdot 0.2\ H_2O$: C 68.24, H 6.24, N 14.74: found: C 68.20, H 6.18, N 14.52; m.p.101-102°C.

Example 8

N-Benzyl-N'-{4-{3-[4-(N-(3,4-dichlorophenyl-N-methyl)aminopropoxy]phenyl}thiazol-2-yl}guanidine,

A solution of N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(3-chloropropoxy)phenyl]thiazol-2-yl}guanidine (0.25 g, 0.48 mmol), [prepared in a similar manner to the intermediate from example 1d], N-3,4-dichlorophenyl-N-methylamine (0.17 g, 0.96 mmol) and sodium iodide (0.072 g, 0.48 mmol) in dimethylformamide was heated at 130-135°C for 4 d. and was cooled. The reaction was diluted with water and was extracted twice with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate), and was evaporated.

Purification by two flash chromatographies, eluting first with 35:65 ethyl acetate:hexanes, then with 2:8 acetone:hexanes, provided a mixture of the title compound and N-benzyl-N'-{4-{3-[3-chloropropoxy]phenyl}thiazol-2-yl}guanidine (0.044 g). Into a solution of this mixture in methanol (1 mL) at -78°C in a reaction tube under argon was condensed 50 drops of ammonia, the tube was sealed and was heated at 45-50°C for 5 d. The reaction was cooled and was evaporated. Purification by flash chromatography, eluting with 35:65 ethyl acetate : hexanes provided the title compound (0.027 g, 10%) as a pale amber glass. Mass Spec. (ES+): M+H (554.2, 556.2). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.2-7.4 (m, 9H), 7.19 (d, J=8.9 Hz, 1H), 6.82 (s, 1H), 6.79 (dd, J=2.3, 9.1 Hz, 1H), 6.71 (d, J=3.0 Hz, 1H), 6.50 (dd, J=3.0, 9.1 Hz, 1H), 4.48 (s, 2H), 3.97 (br s, 2H), 3.35 (t, J=7.0 Hz, 2H), 2.91 (s, 3H), 1.77 (m, 4H) ppm.

Proceeding in the same manner as in Example 8, but substituting the appropriate intermediates for those described above, the following compound was prepared:

Example 9

N-Benzyl-N'-{4-{3-[4-(N-(3,4-dichlorophenyl) -N-methyl)aminobutoxy]phenyl}thiazol-2-yl}guanidine

Mass Spec (ES+): M+H (472.2), m.p. 40-45°C

Example 10

N'-{4-{3-[4-(N-Methyl-N-phenyl)aminobutoxy]phenyl}thiazol-2-yl}guanidine 10a. N-*t*-Butoxycarbonyl-N'-{4-[3-(4-iodobutoxy)phenyl]thiazol-2-yl}guanidine

A mixture of N-*t*-butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine (0.100 g, 0.24 mmol) and sodium iodide (0.039 g, 0.25 mmol) in acetone (5 mL) was refluxed under argon for 48 h. The suspension was cooled, was filtered and was evaporated to provide an approximately 1:1 mixture of N-*t*-butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine and N-*t*-butoxycarbonyl-N'-{4-[3-(4-iodobutoxy)phenyl]thiazol-2-yl}guanidine (0.12 g). ^{1}H-NMR ($CDCl_3$, 400 MHz) : δ 9.9 (br, 1H), 8.8 (br, 1H), 7.3-7.5 (m, 3H), 6.95 (m, 1H), 6.85 (m, 1H), 4.05 (m 2H), 3.63 (t, 0.55H, C$\underline{H}_2$Cl), 3.26 (t, 0.45H, C$\underline{H}_2$I), 1.9-2.1 (m, 4H), 1.5-1.6 (br, 9H) ppm.

10b. N'-{4-{3-[4-(N-Methyl-N-phenyl)aminobutoxy]phenyl}thiazol-2-yl}guanidine

The approximately 1:1 mixture of N-*t*-butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine and N-*t*-butoxycarbonyl-N'-{4-[3-(4-iodobutoxy)phenyl]thiazol-2-yl}guanidine (0.12 g).and N-methylaniline (0.055 mL, 0.48 mmol) in dimethylformamide (3 mL) was heated at 130-135°C for 3 d. The reaction was cooled, was diluted with water and was twice extracted with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate) and was evaporated. Purification by two flash chromatographies , eluting first with 6:4 ethyl acetate:hexanes, then with 35:63 acetone:hexanes, provided the title compound (0.031 g, 33%) as a colorless glass, m.p.111-113°C. Mass Sec. (ES+): M+H 396.1.

Example 11

N-Benzyl-N'-{4-[3-(4-methoxybutoxy)phenyl]thiazol-2-yl}guanidine

11a. N-Benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-methoxybutoxy)phenyl]thiazol-2-yl}guanidine

Starting with 3-(4-methoxybutoxy)acetophenone, the by-product obtained in Example 1a, N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-methoxybutoxy)phenyl]thiazol-2-yl}guanidine was prepared following the procedures described in Example 1, m.p. 70-71°C.

11b. N-Benzyl-N'-{4-[3-(4-methoxybutoxy)phenyl]thiazol-2-yl}guanidine

A solution of N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-methoxybutoxy)phenyl]thiazol-2-yl}guanidine (0.045 g, 0.089 mmol) and trifluoroacetic acid (0.035 mL, 0.45 mmol) in dichloromethane (3 mL) was stirred at room temperature under argon for 7 d. The reaction was diluted with water, was neutralized (sodium bicarbonate), was three times extracted with 5/95 methanol/dichloromethane, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 2:98 methanol:dichloromethane, provided the title compound (0.017 g, 46%) as an oil. Mass Spec. (ES+): M+H 411.2. ^{1}H-NMR ($CDCl_3$, 400 MHz) : δ 7.2-7.4 (m, 8H), 6.80 (m, 2H), 4.48 (m, 2H), 3.98 (t, J=6.1 Hz, 2H), 3.43 (t, J=6.3 Hz, 2H), 3.34 (s, 3H), 1.85 (m, 2H), 1.76 (m, 2H) ppm.

Example 12

N-Benzyl-N'-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine

12a. 3-[4-(N-Methyl-N-phenylaminobutoxy)]acetophenone

A solution of 3-(4-chlorobutoxy)acetophenone (2.98 g, 13.2 mmol), [prepared in example 1a] and N-methylaniline (2.90 mL, 26.4 mmol) in dimethylformamide (30 mL) was heated at 130-140°C for 3 d. and was cooled. The reaction was diluted with water and was extracted twice with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 7:93 ethyl acetate:hexanes provided 3-[4-(N-methyl-N-phenylaminobutoxy)]acetophenone (3.03 g, 77%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 400 MHz) : δ 7.52 (d, J=1.0 Hz, 1H), 7.47 (dd, J=1.4, 2.3 Hz, 1H), 7.36 (t, J=7.9 Hz, 1H), 7.23 (t, J=7.9 Hz, 2H), 7.09 (dd, J=2.3, 6.7 Hz, 1H), 6.70 (m, 2H), 4.03 (t, J=6.0 Hz, 2H), 3.40 (t, J=8.1 Hz, 2H), 2.95 (s, 3H), 2.59 (s, 3H), 1.81 (m, 4H) ppm.

12b. N-{4-[3-(4-N-(4-Bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine

A solution of 3-[4-(N-methyl-N-phenylaminobutoxy)]acetophenone (3.02 g, 10.2 mmol) in dichloromethane (35 mL) at room temperature was treated dropwise over 10 min with a solution of bromine (0.525 mL, 10.2 mmol) in dichloromethane (20 mL), then was stirred for 20 min and was evaporated. The residue was dissolved in absolute ethanol (50 mL) was treated with iminothiobiuret (1.18 g, 10.2 mmol), was refluxed for 24 h, was cooled and was evaporated. Purification by flash chromatography, eluting with 5:95 methanol:dichloromethane, provided N-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine (0.44 g, 9%) as a brown solid, m.p.52-57°C.

12c. N-*t*-Butoxycarbonyl-N'-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine

A mixture of N-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine (0.44 g, 0.92 mmol), di-*t*-butyldicarbonate (0.25 g, 1.15 mmol) and several crystals of 4-(N,N-dimethylamino)pyridine in dichloromethane (5 mL) was stirred at room temperature under

argon for 20h. The reaction was evaporated and was purified by flash chromatography, eluting with 15:85 ethyl acetate:hexanes, to obtain N-*t*-butoxycarbonyl-N'-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine (0.48 g, 90%) as a colorless oil. Mass spec (ES+): M+H (574.2, 576.2).

12d. N-Benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine

A mixture of N-*t*-butoxycarbonyl-N'-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine (0.35 g, 0.65 mmol) and 60% sodium hydride/mineral oil suspension (0.028 g, 0.72 mmol) in dimethylformamide (5 mL) was stirred at room temperature under argon for 0.5 h, then was treated with benzyl bromide (0.085 mL, 0.72 mmol) and was stirred for 3 d. The reaction was diluted with water and was extracted twice with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 7:93 ethyl acetate:hexanes, provided N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine (0.13 g, 43%) as a colorless oil. Mass spec. (ES+): M+H (664.2, 666.2).

12e. N-Benzyl-N'-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine

A solution of N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine (0.15 g, 0.24 mmol) and trifluoroacetic acid (0.095 mL, 1.2 mmol) in dichloromethane (5 mL) was stirred at room temperature under argon for 7 d. The reaction was diluted with water, was neutralized (sodium bicarbonate), was three times extracted with 5/95 methanol/dichloromethane, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 2:98 methanol:dichloromethane, provided the title compound (0.081 g, 60%) as an off-white solid, m.p. 47-50°C.

Analysis calc. for $C_{28}H_{30}BrN_5OS$: C 59.57, H 5.36, N 12.41: found: C 59.49, H 5.37, N 12.18

Example 13

N-Benzyl-N'-{4-[3-(4-N-morpholinobutoxy)phenyl]thiazol-2-yl}guanidine 13a. N-Benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-iodobutoxy)phenyl]thiazol-2-yl}guanidine

A mixture of N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine (0.26 g, 0.51 mmol) and sodium iodide (0.23 g, 1.53 mmol) in acetone (10 mL) was refluxed for 48 h. The reaction was cooled, was filtered and was evaporated to provide N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-iodobutoxy)phenyl]thiazol-2-yl}guanidine (0.25 g, 82%) as a yellow oil. Mass spec. (ES+): M+H 607.1.

13b. N-Benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-N-morpholinobutoxy)phenyl]thiazol-2-yl}guanidine

A solution of N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-iodobutoxy)phenyl]thiazol-2-yl}guanidine (0.25 g, 0.42 mmol) and morpholine (0.185 mL, 2.1 mmol) in dimethylformamide (5 mL) was heated at 135-140°C for 1.5 h . The reaction was cooled, was diluted with water and was extracted twice with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate) and was evaporated. Purification by two flash chromatographies, eluting first with 3:97 methanol:dichloromethane, then with 3:1 ethyl acetate:hexanes, provided N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-N-morpholinobutoxy)phenyl]thiazol-2-yl}guanidine (0.14 g, 60%) as a colorless oil. Mass spec. (ES+): M+H 566.2.

13c. N-Benzyl-N'-{4-[3-(4-N-morpholinobutoxy)phenyl]thiazol-2-yl}guanidine

A solution of N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-N-morpholinobutoxy)phenyl]thiazol-2-yl}guanidine (0.14 g, 0.25 mmol) and trifluoroacetic acid (2 mL) in dichloromethane (2 mL) was stirred at room temperature for 5 h. The reaction was diluted with water, was neutralized (sodium bicarbonate), was three times extracted with 5:95 methanol:dichloromethane, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 1:9 methanol : dichloromethane provided the title compound (0.076 g, 65%) as an amber glass. Mass spec. (ES+): M+H 466.3.

Analysis calc. for $C_{25}H_{31}N_5O_2S \cdot 0.4\ H_2O$: C 63.51, H 6.78, N 14.81: found: C 63.56, H 6.67, N 14.51.

Example 14

N-Benzyl-N'-{4-[3-(4-N-piperazinobutoxy)phenyl]thiazol-2-yl}guanidine 14a. N-*t*-Butoxycarbonyl-N'-{4-[3-(4-iodobutoxy)phenyl]thiazol-2-yl}guanidine

A mixture of N-*t*-butoxycarbonyl-N'-{4-[3-(4-chlorobutoxy)phenyl]thiazol-2-yl}guanidine (3.52 g, 8.27 mmol) and sodium iodide (3.70 g, 24.8 mmol) in acetone (75 mL) was refluxed for 24 h. The reaction was cooled, was filtered through Celite, washing with ether, and was evaporated to provide N-*t*-butoxycarbonyl-N'-{4-[3-(4-iodobutoxy)phenyl]thiazol-2-yl}guanidine (2.52 g, 59%) as a yellow oil. Mass spec. (ES+): M+H 517.0.

14b. N-Benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-bromobutoxy)phenyl]thiazol-2-yl}guanidine

A mixture of N-*t*-butoxycarbonyl-N'-{4-[3-(4-iodobutoxy)phenyl]thiazol-2-yl}guanidine (2.52 g, 4.88 mmol) and 60% sodium hydride/mineral oil suspension (0.215 g, 5.37 mmol) in dimethylformamide (30 mL) was treated with benzyl bromide (0.65 mL, 5.37 mmol) and was stirred for 2 h. The reaction was diluted with water and was extracted twice with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 5:95 ethyl acetate:hexanes, provided N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-bromobutoxy)phenyl]thiazol-2-yl}guanidine (1.40 g, 51%) as a waxy white solid, m.p. 80-81°C.

14c. N-Benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-(N-t-butoxycarbonylpiperazinobutoxy)phenyl]thiazol-2-yl}guanidine

A solution of N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-bromobutoxy)phenyl]thiazol-2-yl}guanidine (0.24 g, 0.42 mmol) and N-*t*-butoxycarbonylpiperazine (0.39 g, 2.1 mmol) in dimethylformamide (5 mL) was heated at 135-140°C for 3 h. The reaction was cooled, was diluted with water and was extracted twice with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate) and was evaporated. Purification by two flash chromatographies, eluting first with 3:97 methanol:dichloromethane, then with 3:1 ethyl acetate:hexanes, provided N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-N-*t*-

butoxycarbonylpiperazinobutoxy)phenyl]thiazol-2-yl}guanidine (0.29 g, 100%) as a colorless oil. Mass spec. (ES+): (M+H-2BOC) 465.4.

14d. N-Benzyl-N'-{4-[3-(4-N-piperazinobutoxy)phenyl]thiazol-2-yl}guanidine

A solution of N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[3-(4-N-*t*-butoxycarbonylpiperazinobutoxy)phenyl]thiazol-2-yl}guanidine (0.29 g, 0.42 mmol) and trifluoroacetic acid (1.5 mL) in dichloromethane (1.5 mL) was stirred at room temperature for 5 h. The reaction was diluted with water, was neutralized (sodium bicarbonate), was three times extracted with 5/95 methanol/dichloromethane, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 0.2:2:8 ammonium hydroxide:methanol:dichloromethane, provided the title compound (0.11 g, 58%) as a waxy, pale pink solid, m.p. 130-134°C.

Analysis calc. for $C_{25}H_{32}N_6OS \cdot 0.65\ H_2O$: C 63.04, H 7.05, N 17.64: found: C 63.00, H 6.73, N 17.45

Example 15

N-Benzyl-N'-{4-{4-[3-(N-(3,4-dichlorophenyl)-N-methyl)aminopropoxy]phenyl}thiazol-2-yl}urea

15a. 2-Amino-4-[4-(3-chloropropoxy)phenyl]thiazole

A suspension of 4-(3-chloropropoxy)acetophenone (2.43 g, 11.4 mmol) [prepared following the procedure described in Example 1a, substituting the appropriate reagents] in tetrahydrofuran (45 mL) at room temperature was treated portionwise with phenyltrimethylammonium tribromide (4.29 g, 11.4 mmol), was stirred 1 h and was filtered. The filtrate was evaporated. The residue was dissolved in ethanol (50 mL), was treated with thiourea (0.87 g, 11.4 mmol) and was refluxed for 5 h, stirred at room temperature for 20 h, and was evaporated. Purification by flash chromatography, eluting with 5:95 methanol:dichloromethane, provided 2-amino-4-[4-(3-chloropropoxy)phenyl]thiazole (2.27 g, 74%) as a yellow solid, m.p.130-132°C.

15b. N-Benzyl-N'-{4-{4-[3-chloropropoxy]phenyl}thiazol-2-yl}urea

A suspension of 2-amino-4-[4-(3-chloropropoxy)phenyl]thiazole (0.13 g, 0.5 mmol) in toluene (5 mL) was treated with benzylisocyanate (0.070 mL, 0.55 mmol) and was stirred at 80-85°C for 5 h and at room temperature for 18 h. The reaction was diluted

with water, was extracted three times with dichloromethane, was dried (magnesium sulfate), and was evaporated. Purification by flash chromatography, eluting with 2:8 ethyl acetate:hexanes provided N-benzyl-N'-{4-{4-[3-chloropropoxy]phenyl}thiazol-2-yl}urea (0.12 g, 59%) as a white solid, m.p.160-161°C.

15c. <u>N-Benzyl-N'-{4-{4-[3-iodopropoxy]phenyl}thiazol-2-yl}urea</u>

A mixture of N-benzyl-N'-{4-{4-[3-chloropropoxy]phenyl}thiazol-2-yl}urea (0.17 g, 0.43 mmol) and sodium iodide (0.32 g, 2.15 mmol) in acetone (5 mL) was refluxed for 24 h, was cooled and was evaporated. The residue was triturated with ether and was filtered. The filtrate was evaporated to obtain N-benzyl-N'-{4-{4-[3-iodopropoxy]phenyl}thiazol-2-yl}urea (0.17 g, 81%) as a yellow oil.

15d. <u>N-Benzyl-N'-{4-{4-[3-(N-(3,4-dichlorophenyl)-N-methyl)aminopropoxy]phenyl}thiazol-2-yl}urea</u>

A solution of (0.24 g, 0.42 mmol) N-benzyl-N'-{4-{4-[3-iodopropoxy]phenyl}thiazol-2-yl}urea (0.17 g, 0.35 mmol) and N-(3,4-dichlorophenyl)-N-methylamine (0.13g, 0.7 mmol) in dimethylformamide (3 mL) was heated at 135-140°C for 8 h, then at room temperature for 18 h. The reaction was diluted with water and was extracted twice with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate) and was evaporated. Purification by two flash chromatographies, eluting first with 3:7 ethyl acetate:hexanes, then with 25:75 acetone:hexanes, followed by preparative thin layer using 3:7 acetone:hexanes provided N-benzyl-N'-{4-{4-[3-(N-(3,4-dichlorophenyl)-N-methyl)aminopropoxy]phenyl}thiazol-2-yl}urea (0.015 g, 8%), as an off-white foam, m.p. 65-69°C. Mass spec. (ES+): M+H (541.2, 543.2)

Example 16

N-Benzyl-N'-{4-{4-[3-[N-carbobenzyloxy-N-(3,4-dichlorophenyl)]aminopropoxy]phenyl}thiazol-2-yl}guanidine

16a. N-Benzyl-N-*t*-butoxycarbonyl-N'-{4-{4-[3-[N-carbobenzyloxy-N-(3,4-dichlorophenyl)]aminopropoxy]phenyl}thiazol-2-yl}guanidine

A solution of N-carbobenzyloxy-3,4-dichloroaniline (0.039 g, 0.13 mmol) and 60% sodium hydride/mineral oil (0.006 g, 0.15 mmol) in dimethylformamide (2 mL) was stirred 15 min. N-benzyl-N-*t*-butoxycarbonyl-N'-{4-[4-(3-iodopropoxy)phenyl]thiazol-2-yl}guanidine (0.077 g, 0.13 mmol) (prepared as described in example 6a, substituting the appropriate intermediate) in dimethylformamide (1 mL) was added and the reaction was stirred for 5h at room temperature. The reaction was diluted with water and was twice extracted with ethyl acetate. The combined organic phase was washed three times with water, once with brine, was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 15:85 ethyl acetate : hexanes provided N-benzyl-N-*t*-butoxycarbonyl-N'-{4-{4-[3-[N-carbobenzyloxy-N-(3,4-dichlorophenyl)]aminopropoxy]phenyl}thiazol-2-yl}guanidine (0.053 g, 53%) as a pale yellow film. Mass spec. (ES+): M+H (760.4, 762.3).

16b. N-Benzyl-N'-{4-{4-[3-[N-carbobenzyloxy-N-(3,4-dichlorophenyl)]aminopropoxy]phenyl}thiazol-2-yl}guanidine

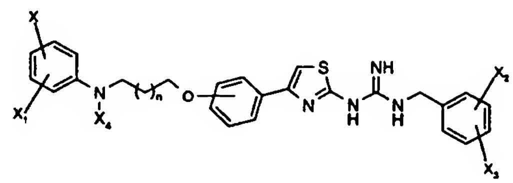
A solution of N-benzyl-N-*t*-butoxycarbonyl-N'-{4-{4-[3-[N-carbobenzyloxy-N-(3,4-dichlorophenyl)]aminopropoxy]phenyl}thiazol-2-yl}guanidine (0.063 g, 0.083 mmol) in dichloromethane (2 mL) and trifluoroacetic acid (2 mL) was stirred at room temperature under argon for 3h. The reaction was neutralized with sodium bicarbonate (aq.), was extracted three times with dichloromethane, was dried (magnesium sulfate), and was evaporated. Purification by flash chromatography, eluting with 35:65 ethyl acetate : hexanes, provided the title compound (0.013 g, 24%) as a colorless film. Mass spec. (ES+): M+H (660.3, 662.3). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.2-7.6 (m, 14H), 7.09 (d, J=8.3 Hz, 1H), 6.75 (d, J=8.2 Hz, 2H), 6.70 (s, 1H), 5.13 (s, 2H), 4.49 (s, 2H), 3.98 (t, J=5.8 Hz, 2H), 3.89 (t, J=7.0 Hz, 2H), 2.05 (m, 2H), 2.0 (br, 2H) ppm.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the

particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

We claim:

1. A compound of Formula I:



(I)

wherein:

X, X_1, X_2, and X_3 are independently selected from -H, -C_{1-6}alkyl, -C_{1-6}alkyl substituted by 1-3 fluorines, -C_{3-7}cycloalkyl, -CN, -C(O)R_1, -C(O)OR_1, -C(O)NR_1R_2, -C(NR_1)NR_1R_2, -C(NCN)NR_1R_2, -C(NCN)SR_3, -NO_2, -NR_1SO_2R_3, -NR_1C(O)R_1, -NR_1R_2, -NR_1(C=NR_1)NR_1R_2, -NR_1C(O)NR_1R_2, -NR_1C(O)R_1, -NR_1C(O)OR_3, -NR_1C(NCN)SR_3, -NR_1C(NCN)NR_1R_2, -NR_1C(O)C(O)NR_1R_2, -NR_1C(O)C(O)R_2, -Cl, -Br, -I, -F, -OR_1, -O$(CH_2)_q$OR_3, -O$(CH_2)_2$OH, -OC(O)R_1, -O$(CH_2)_q$C(O)NR_1R_2, -O$(CH_2)_q$C(O)R_1, -SR_1, -SO_2NR_1R_2 or -S$(O)_m R_3$;

m is 0, 1 or 2;

q is 1 or 2;

n is 0 to 2;

R_1 is -H, -C_{1-6}alkyl, -CF_3 or -CH_2CF_3; or when R_1 and R_2 are taken together as NR_1R_2, they may together with the nitrogen form a 5 to 7 membered ring comprised of carbon or carbon and one or more additional heteroatoms selected from O, N, or S;

R_2 is H, -C_{1-6}alkyl, -CF_3 or -CH_2CF_3;

R_3 is -C_{1-6}alkyl, -CF_3 or -CH_2CF_3; and

X_4 is -H, -C_{1-6}alkyl , -C_{3-7}cycloalkyl, -COAr, -COOC_{1-6}alkyl, or COOAr;

and pharmaceutically acceptable salts, hydrates and solvates thereof.

2. A compound according to Claim 1 wherein:

X, X_1, X_2,and X_3 are independently H or halogen;

X_4 is CH_3 or Cbz; and

n=1 or 2.

3. A compound according to Claim 1 wherein:
X, X_1, X_2,and X_3 are independently H or Cl; and
X_4 is CH_3.

4. A compound according to Claim 3 wherein:
X and X_1 are Cl;
X_2,and X_3 are H;
X_4 is $-CH_3$; and
n=1.

5. A compound according to Claim 1 selected from the group consisting of:
N-Benzyl-N'-{4-{3-[4-(N-methyl-N-phenyl)aminobutoxy]phenyl}thiazol-2-yl}guanidine;
N-Benzyl-N'-{4-{3-[4-(N-(3,4-dichlorophenyl-N-methyl)aminopropoxy]phenyl}thiazol-2-yl}guanidine;
N-Benzyl-N'-{4-[3-(4-N-(4-bromophenyl)-N-methylaminobutoxy)phenyl]thiazol-2-yl}guanidine;
N-Benzyl-N'-{4-[3-(4-N-piperazinobutoxy)phenyl]thiazol-2-yl}guanidine;
N-Benzyl-N'-{4-{4-[3-(N-(3,4-dichlorophenyl)-N-methyl)aminopropoxy]phenyl}thiazol-2-yl}urea; and
N-Benzyl-N'-{4-{4-[3-[N-carbobenzyloxy-N-(3,4-dichlorophenyl)]aminopropoxy]phenyl}thiazol-2-yl}guanidine.

6. A pharmaceutical composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.

7. A pharmaceutical composition comprising a compound according to Claim 5 and a pharmaceutically acceptable carrier, diluent or excipient.

8. A use of a compound according to Claims 1 to 5 for manufacture of a medicament for inhibiting a protease selected from the group consisting of a cysteine protease and a serine protease.

9. A use according to Claim 8 wherein said protease is a cysteine protease.

10. A use according to Claim 9 wherein said cysteine protease is cathepsin K.

11. A use of a compound according to Claims 1 to 5 for manufacture of a medicament for treating a disease characterized by bone loss.

12. A use according to Claim 11 wherein said disease is osteoporosis.

13. A use according to Claim 11 wherein said disease is periodontitis.

14. A use according to Claim 11 wherein said disease is gingivitis.

15. A use of a compound according to Claims 1 to 5 for manufacture of a medicament for treating a disease characterized by excessive cartilage or matrix degradation.

16. A use according to Claim 15 wherein said disease is osteoarthritis.

17. A use according to Claim 15 wherein said disease is rheumatoid arthritis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/18289

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 277/42, 417/12; A61K 43/78
US CL :548/193; 544/369; 514/370
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/193; 544/369; 514/370

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database WPIDS on STN, Derwent Publications LTD., (Columbus Ohio), AN 85-029005, JP 59225172 A (YAMANOUCHI PHARM CO LTD), Abstract, 18 December 1984.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"B" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 NOVEMBER 1998	24 DEC 1998

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ROBERT GERSTL JAB for
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/18289

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-17
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.